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The Magdalen Centre
The Oxford Science Park
Oxford, OX4 4GA

Patents ADP number *(if you know it)* — 7244478003

If the applicant is a corporate body, give the country/state of its incorporation — United Kingdom

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5. Name of your agent *(if you have one)* — Tracy A Burns

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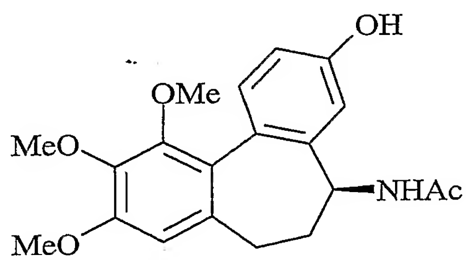
CHEMICAL PROCESSES & INTERMEDIATES

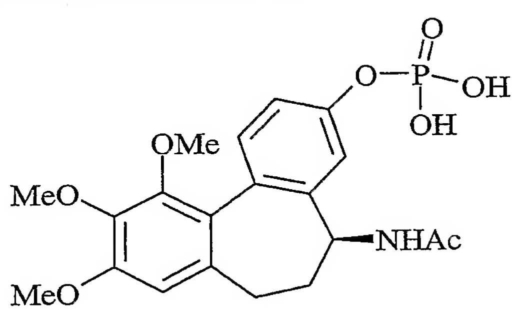
The present invention relates to processes for synthesising *N*-((*S*)-3-hydroxy 9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a*,*c*]cyclohepten-5-yl)-acetamide (hereafter ZD6126 Phenol) from allocolchicine or an ester derivative thereof, to intermediates used in such processes, to processes for the manufacture of such intermediates and to the use of said intermediates in the manufacture of ZD6126 Phenol.

ZD6126 Phenol is also know as N-acetylcolchinol:



ZD6126 Phenol

and is an intermediate useful in the synthesis of (5*S*)-5-(acetylamino)-9,10,11-trimethoxy-6,7-dihydro-5*H*-dibenzo[*a*,*c*]cyclohepten-3-yl dihydrogen phosphate or N-acetylcolchinol-O-phosphate (hereafter ZD6126):



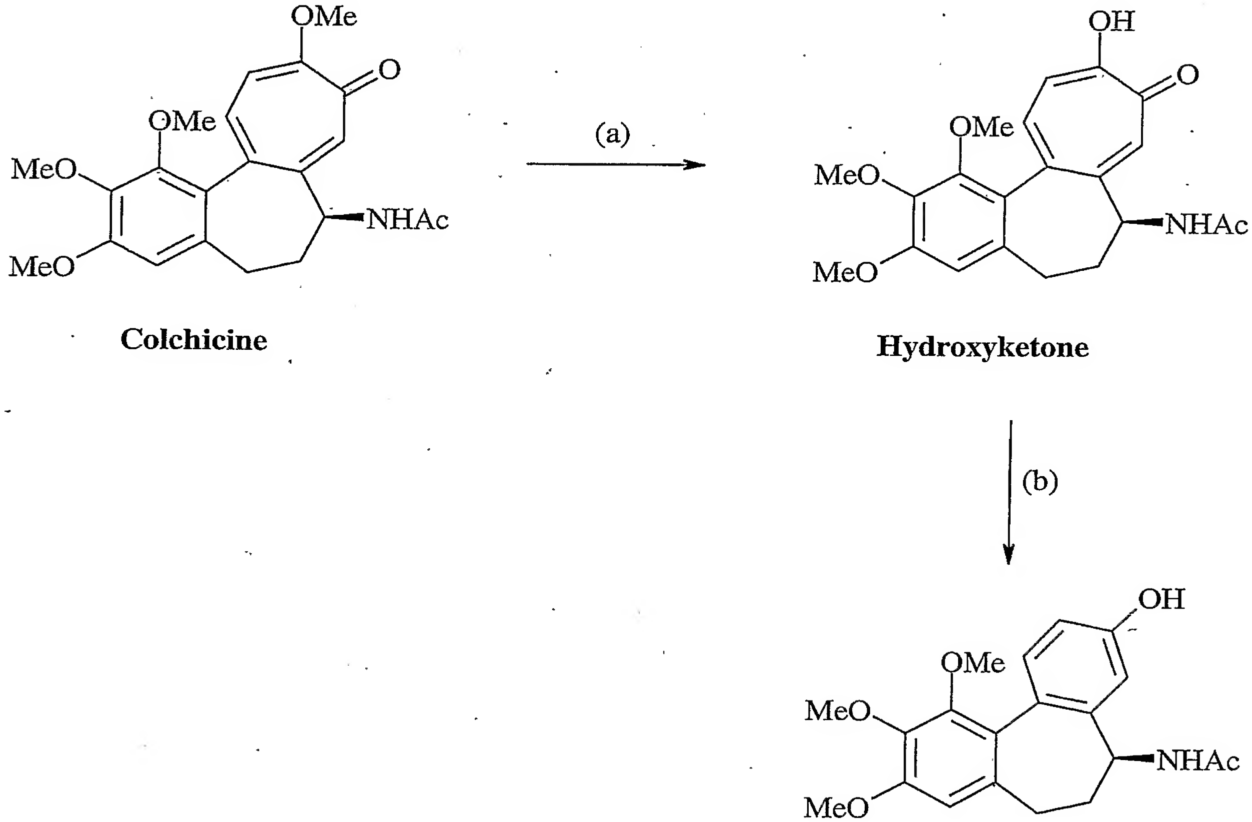
ZD6126

a potent vascular targeting agent.

ZD6126 is described in International Patent Application Publication No. WO 99/02166 (Example 1). It has been reported that ZD6126 selectively disrupts tumour vasculature leading to vessel occlusion and extensive tumour necrosis (Davis, P.D., Hill, S.A., Galbraith, S.M., *et al.*, *Proc. Am. Assoc. Cancer Res.*, 2000; 41: 329). ZD6126 is therefore useful in the treatment of cancer.

WO 99/02166 describes a synthesis of ZD6126 Phenol from colchicine which comprises (a) an acid hydrolysis using hydrochloric acid at a temperature of at or near 100°C,

followed by (b) treatment of the resulting hydroxy ketone intermediate with alkaline hydrogen peroxide to give ZD6126 Phenol. This is illustrated in Scheme A.



Colchicine **Hydroxyketone** **ZD6126 Phenol**

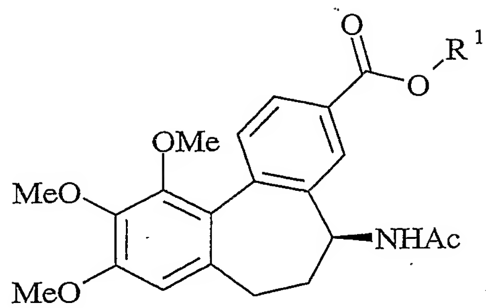
Scheme A

Santavy, F., in Collect. Czech. Chem. Commun., 1949, 14 532-535 reports yields for this synthesis of 79% for step (a) and 25% for step (b) leading to an overall yield of 19%. This is obviously a less than ideal synthesis for use on a large scale.

The present invention relates to a novel process for the synthesis of ZD6126 Phenol from allocolchicine or an ester derivative thereof via an alcohol which gives a surprisingly high yield of 75% (67% from colchicine).

Allocolchicine or an ester derivative thereof may be prepared from colchicine. For example allocolchicine itself can be prepared in 90% yield by treatment of colchicine with sodium methoxide in methanol (Fernholz, V., Justus Liebigs Ann., 1950, 568, 63-72).

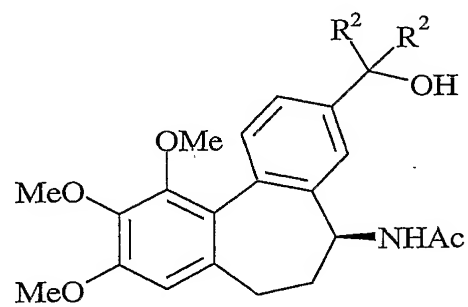
According to the present invention there is provided a process for the preparation of ZD6126 Phenol from allocolchicine or an ester derivative thereof of formula (I):



(I)

wherein R^1 is C_{1-6}alkyl or aryl; which comprises:

a) reacting said allocolchicine or an ester derivative thereof of formula (I) with a suitable organometallic reagent and / or a suitable reducing agent; in one or more ethereal solvents to form ZD6126 Alcohol of formula (II):



(II)

wherein R^2 are each independently hydrogen, C_{1-4}alkyl or aryl; and

b) reacting ZD6126 Alcohol of formula (II) with an acid catalyst and an oxidising agent.

For the avoidance of doubt, the phrase "suitable organometallic reagent and / or a suitable reducing agent" may be selected such that the two R^2 groups introduced are the same or different.

The term "aryl" refers to a 4-10 membered aromatic mono or bicyclic ring containing 0 to 5 heteroatoms independently selected from nitrogen, oxygen or sulphur wherein said aryl may be optionally substituted. Suitable optional substituents for "aryl" include halo, C_{1-6}alkyl, C_{1-6}alkoxy. Examples of "aryl" include phenyl; phenyl substituted by halo, C_{1-6}alkyl or C_{1-6}alkoxy; and certain herteroaromatics, for example pyridyl. In particular "aryl" refers to phenyl.

In this specification the term "alkyl" includes both straight and branched chain alkyl groups but references to individual alkyl groups such as "propyl" are specific for the straight chain version only. For example, "C_{1-6}alkyl" and "C_{1-4}alkyl" includes propyl, isopropyl and t-butyl. However, references to individual alkyl groups such as 'propyl' are specific for the

straight chained version only and references to individual branched chain alkyl groups such as 'isopropyl' are specific for the branched chain version only. The term "halo" refers to fluoro, chloro, bromo and iodo. Examples of "C_{1-6}alkoxy" include methoxy, ethoxy and propoxy.

Particularly, in the formation of ZD6126 Alcohol from allocolchicine or an ester derivative thereof, the allocolchicine or ester derivative thereof is added to >3 mole equivalents of the suitable organometallic reagent and / or suitable reducing agent, preferably maintaining the reaction temperature below ambient.

In a compound of formula (I) when R^1 is methyl this is allocolchicine. Suitably R^1 is C_{1-4}alkyl. In another aspect R^1 is methyl or ethyl. In a further aspect R^1 is methyl.

Particular values for R^2 are C_{1-4}alkyl. More particular values for R^2 are hydrogen, methyl, ethyl, butyl, *t*-butyl and phenyl. In one aspect of the invention both R^2 are methyl. In another aspect of the invention one or both of the groups R^2 can be hydrogen.

Suitable organometallic reagents are those that introduce an R^2 group that is C_{1-4}alkyl or aryl. Examples of suitable organometallic reagents for use in the reactions described herein include methyl lithium, methyl magnesium chloride, methyl magnesium bromide, ethyl magnesium chloride, ethyl magnesium bromide, butyl lithium and phenyllithium. More particularly the organometallic reagent is methyl lithium.

Suitable reducing agents are those that introduce an R^2 group that is hydrogen. Examples of suitable reducing agents for use in the reactions described herein include lithium aluminium hydride, di-isobutyl aluminium hydride or sodium borohydride.

In one aspect of the invention one or more suitable organometallic reagents are used in step a). This results in a tertiary ZD6126 Alcohol.

In another aspect of the invention a suitable organometallic reagent and a suitable reducing agent are used in step a). In the first instance allocolchicine or an ester derivative thereof of formula (I) is converted into a ketone by reaction with one equivalent of a suitable organometallic reagent, for example methyl lithium, ethyl lithium, methyl magnesium chloride, methyl magnesium bromide, ethyl magnesium chloride, ethyl magnesium bromide, butyl lithium or phenyllithium. The ketone is then converted to ZD6126 Alcohol by reaction with a suitable reducing agent such as lithium aluminium hydride, di-isobutyl aluminium hydride or sodium borohydride. This results in a secondary ZD6126 Alcohol.

In a further aspect of the invention one or more suitable reducing reagents are used in step a). This results in primary ZD6126 Alcohol.

In another aspect of the invention step a) might be conducted in the presence of an alkali metal halide. Particular alkali metal halides are lithium chloride or lithium bromide. A more particular alkali metal halide is lithium bromide.

Particular ethereal solvents for use in the reactions described herein are tetrahydrofuran, diethyl ether, diethoxymethane, 2-ethoxyethylether, 2-methoxyethyl ether and dimethoxy ethane or a mixture of one or more of these solvents. Yields for step a) conducted in various ethereal solvents are given in Table 1. Conveniently, the ethereal solvent used in the reactions described herein is a mixture of tetrahydrofuran and diethoxymethane. In another aspect, more particularly the ethereal solvent used in the reactions described herein is diethyl ether. In another aspect, more particularly the ethereal solvent used in the reactions described herein is 2-ethoxyethylether. In another aspect, more particularly the ethereal solvent used in the reactions described herein is 2-methoxyethyl ether. In another aspect, more particularly the ethereal solvent used in the reactions described herein is dimethoxy ethane. In another aspect, more particularly the ethereal solvent used in the reactions described herein is tetrahydrofuran.

Solvent	**% Conversion to Alcohol**
Tetrahydrofuran	91
Diethyl ether	90
Dimethoxy ethane	65
2-Ethoxyethyl ether	65
2-Methoxyethyl ether	80

Table 1

The second step of the process, Step b) is an acid catalysed oxidative rearrangement to form ZD6126 Phenol plus a carbonyl compound. Particular oxidising agents for use in the reactions described herein are peroxides, hydroperoxides or peroxyacids. More particularly the oxidising agent is hydrogen peroxide.

A range of acids haven been shown to be effective catalysts for step b). Particular acid catalysts for use in the reactions described herein are methanesulfonic acid, trifluoroacetic acid or toluenesulfonic acid. More particularly the acid catalyst is methanesulphonic acid.

Examples of acid catalysts that have been evaluated are shown in Table 2.

Acid catalyst	Conversion to Phenol/ HPLC area %
Trifloroacetic acid	51
pTSA/toluene	76
pTSA/water	94
$MeSO_3H$	94-96

Table 2

Suitable solvents for use in step b) are toluene, xylene, chlorobenzene, trifluorotoluene, butyl acetate or tetrahydrofuran.

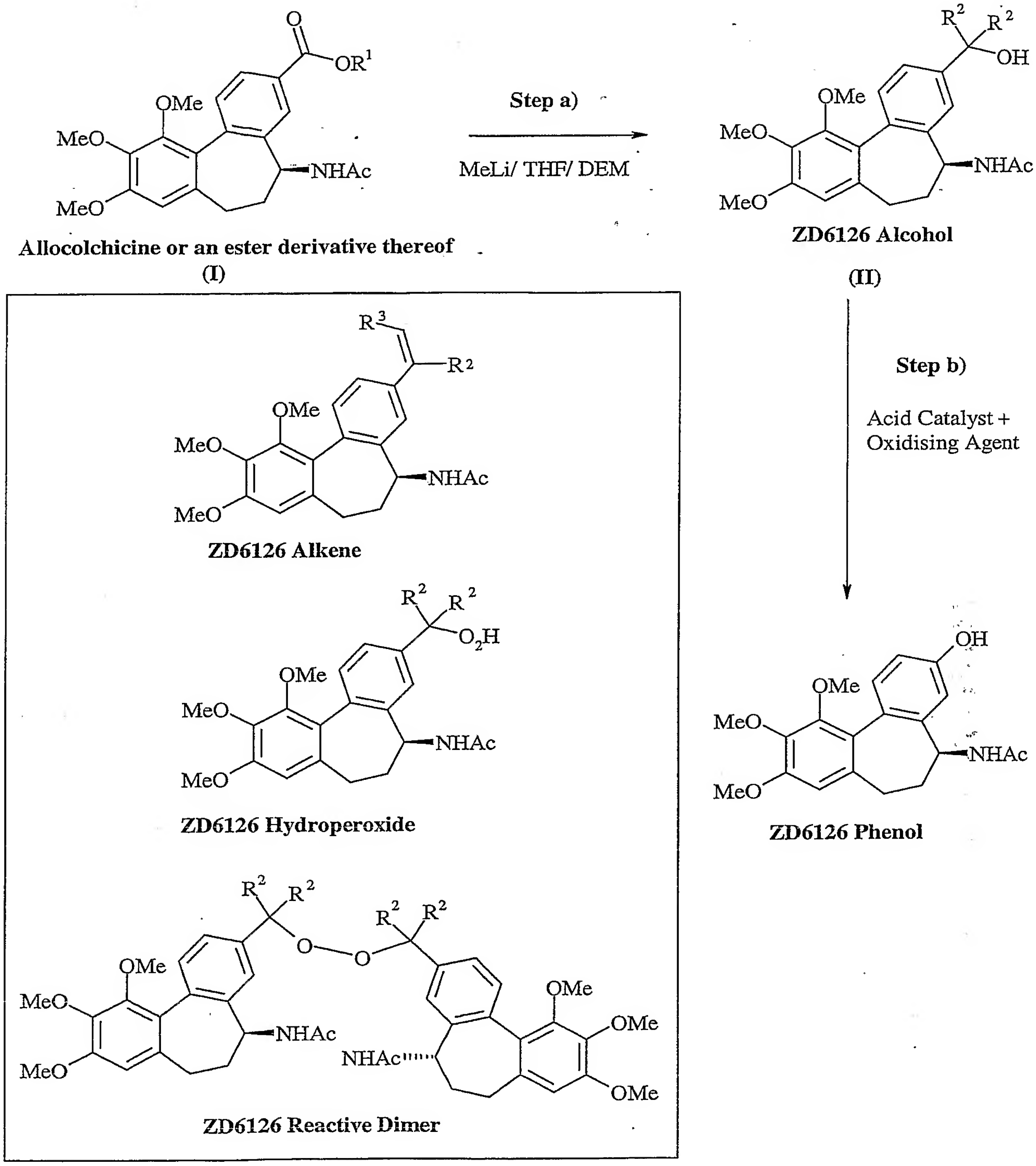
Examples of solvents that have been investigated for the conversion of TA to Phenol:

Solvent	% Conversion to Phenol
Butyl acetate	74
Toluene	95
Trifluoromethylphenyl	78
Methyl *t*-butyl ether	87
Chlorobenzene	91
Xylene	93

The conversion of the ZD6126 Alcohol to ZD6126 Phenol may be effected in one stage, or two consecutive stages.

Conveniently, the ethereal solution of ZD6126 Alcohol, as prepared in Step a) is converted into a solution in toluene (or other solvent) by azeotropic distillation. Direct transformation of ZD6126 Alcohol into ZD6126 Phenol is then brought about by dual addition of an oxidizing agent, more particularly hydrogen peroxide, and an acid catalyst, more particularly methanesulphonic acid, at an elevated temperature, for example 50°C.

In a further aspect of the invention, ZD6126 Alkene, ZD6126 Hydroperoxide and ZD6126 Reactive Dimer are known by-products (and possible intermediates) of the reaction. The present inventions have demonstrated that each of these compounds can be converted into ZD6126 Phenol. These compounds are thus provided as a further feature of the invention.



Scheme B

R^3 is hydrogen or C_{1-3}alkyl and R^3 is always one carbon shorter than the C_{1-4}alkyl R^2 group that formed it. For example if said R^2 was methyl, R^3 is hydrogen. If R^2 was ethyl, R^3 is methyl. If R^2 was propyl, R^3 is ethyl and so on.

The skilled person will appreciate that ZD6126 Alkene will not be formed unless at least one R^2 in the ZD6126 Alcohol is C_{1-4}alkyl. However, conversion of ZD6126 Alcohol to ZD6126 Phenol will occur even if neither R^2 is C_{1-4}alkyl.

In one aspect of the invention, the conversion of allocolchicine or an ester derivative thereof into ZD6126 Phenol may be effected in one stage, without isolation of ZD6126 Alcohol. In another aspect of the invention allocolchicine or an ester derivative thereof is converted into ZD6126 Alcohol, which is isolated as a solid. In a further aspect of the invention ZD6126 Alcohol is converted into ZD6126 Phenol in a single stage. In another aspect of the invention ZD6126 Alcohol is converted into ZD6126 Hydroperoxide, which is isolated. In a further aspect of the invention ZD6126 Hydroperoxide is converted into ZD6126 Phenol. In another aspect of the invention ZD6126 Alcohol is converted into ZD6126 Alkene, which is isolated. In a further aspect of the invention ZD6126 Alkene is converted into ZD6126 Phenol. In another aspect of the invention ZD6126 Alcohol is converted into ZD6126 Reactive Dimer which is isolated. In a further aspect of the invention ZD6126 Reactive Dimer is converted into ZD6126 Phenol.

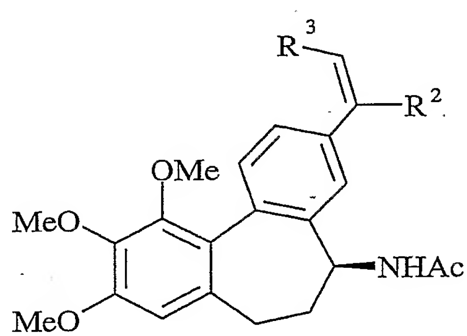
Certain intermediates described herein are novel and are provided as another aspect of the present invention.

According to another aspect of the present invention there is provided ZD6126 Alcohol of formula **(II)** (as depicted above) with the proviso that R^2 cannot both be methyl or both be hydrogen.

According to another aspect of the present invention there is provided a process for the preparation of a ZD6126 Alcohol of the formula **(II)** wherein R^2 are each independently hydrogen, C_{1-4}alkyl or aryl which comprises reacting a compound of formula **(I)** (as depicted above - allocolchicine or an ester derivative thereof) with a suitable organometallic reagent and/or suitable reducing agent in one or more ethereal solvents.

According to another aspect of the present invention there is provided the use of a ZD6126 Alcohol of formula **(II)** in a process for the preparation of ZD6126 Phenol.

According to another aspect of the present invention there is provided ZD6126 Alkene of formula **(III)**:



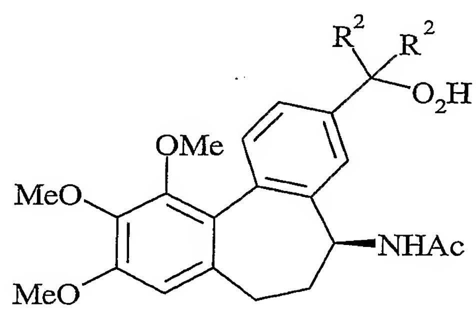
(III)

wherein R^2 is hydrogen, C_{1-4}alkyl or aryl and R^3 is hydrogen or C_{1-3}alkyl.

According to another aspect of the present invention there is provided a process for the preparation of ZD6126 Alkene of formula **(III)** (as depicted above) which comprises reacting a ZD6126 Alcohol of the formula **(II)** wherein at least one R^2 group is C_{1-4}alkyl with an acid catalyst.

According to another aspect of the present invention there is provided the use of ZD6126 Alkene of formula **(III)** in a process for the preparation of ZD6126 Phenol.

According to another aspect of the present invention there is provided ZD6126 Hydroperoxide of formula **(IV)**:



(IV)

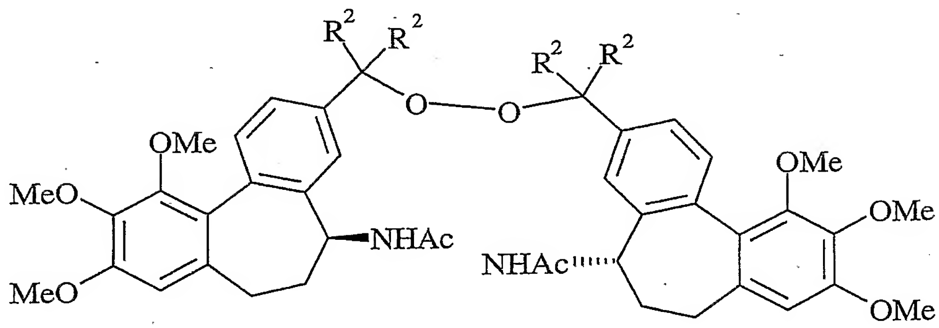
wherein R^2 are each independently hydrogen, C_{1-4}alkyl or aryl.

According to another aspect of the present invention there is provided a process for the preparation of ZD6126 Hydroperoxide of formula **(IV)** (as depicted above) which comprises reacting a ZD6126 Alcohol of the formula **(II)** with an acid catalyst and oxidising agent in the presence of a solvent.

According to another aspect of the present invention there is provided a process for the preparation of ZD6126 Hydroperoxide of formula **(IV)** (as depicted above) wherein at least one R^2 group is C_{1-4}alkyl which comprises reacting a ZD6126 Alkene of formula **(III)** with an oxidising agent in the presence of a solvent.

According to another aspect of the present invention there is provided the use of ZD6126 Hydroperoxide of formula **(IV)** in a process for the preparation of ZD6126 Phenol.

According to another aspect of the present invention there is provided ZD6126 Reactive Dimer of formula **(V)**:



(V)

wherein R^2 are each independently hydrogen, C_{1-4}alkyl or aryl.

According to another aspect of the present invention there is provided a process for the preparation of ZD6126 Reactive Dimer of formula **(V)** (as depicted above) which comprises reacting ZD6126 Alcohol with an oxidizing agent.

According to another aspect of the present invention there is provided the use of ZD6126 Reactive Dimer in a process for the preparation of ZD6126 Phenol.

Examples

The invention will now be illustrated in the following non limiting examples, in which standard techniques known to the skilled chemist and techniques analogous to those described in these examples may be used where appropriate, and in which, unless otherwise stated:

(i) evaporations were carried out by rotary evaporation in vacuo and work up procedures were carried out after removal of residual solids such as drying agents by filtration;

(ii) all reactions were carried out under an inert atmosphere at ambient temperature, typically in the range 18-25°C, with solvents technical grade under anhydrous conditions, unless otherwise stated;

(iii) the structures of the end products of the formula **(I)** were generally confirmed by nuclear (generally proton) magnetic resonance (NMR) and mass spectral techniques; magnetic resonance chemical shift values were measured in deuterated dimethyl sulphoxide (unless otherwise stated) on the delta scale (ppm downfield from tetramethylsilane); proton data is quoted unless otherwise stated; spectra were recorded on a on a Bruker DRX500 spectrometer; and peak multiplicities are shown as follows: s, singlet; d, doublet; dd, double doublet; t, triplet; tt, triple triplet; q, quartet; tq, triple quartet; m, multiplet; br, broad; LCMS were recored on a Waters ZQ Mass Spec Detector, LC column was a SB C8 150mm x 3.0 mm 3.5um (Agilent Zorbax), detection with a HP1100 with a Diode Array Detector; unless otherwise stated the mass ion quoted is $[M + H]^+$;

(iv) the following abbreviations may be used hereinbefore or hereinafter:-

THF	tetrahydrofuran; and
butyl acetate	BuOAc; and

(v) the term Rel. Vols (or Vols) refers to the relative amount of solvent used in millilitres, relative to the amount of the main reaction substrate in grams.

Example 1

Allocolchicine to ZD6126 Alcohol (wherein R^2 are both methyl)

To a stirred solution of methyllithium (4 mole equivalents of a 3 M solution) in diethoxymethane and THF (3 Rel. Vols), at < -5°C, was added a slurry of allocolchicine in THF (3-7 Rel. Vols), over 1 hour. After a further 1 hour (or when no allocolchicine remained by HPLC) the mixture was treated, first with aqueous THF (3 mole equiv. water made-up to 1 Rel Vol with THF), then with water (4 Rel. Vols). Toluene (15 Rel. Vols) was then added and the aqueous layer was removed. The mixture was washed further with water (3 x 2 Rel. Vols). mixture and was then distilled under reduced pressure to a volume of 5 Rel. Vols. A further charge of toluene (20 Rel. Vols) was added to the mixture and it was further distilled under reduced pressure to a volume of about 10 Rel. Vols. The mixture was then cooled and the solid was filtered off, washed with toluene (2 Rel. Vols) and then dried in a vacuum oven at 50°C. The isolated yield of ZD6126 Alcohol was 85%: MS, 382 $[M - OH]^+$ - (100%); δ^H ppm (500 MHz, DMSO-D_6) 1.46 (3 H, s, CHC**H**$_3$), 1.49 (3 H, s, CHC**H**$_3$), 1.89 (3 H, s, COC**H**$_3$), 1.89 (1 H, m, CH$_2$C**H**$_2$), 2.04 (1 H, m, CH$_2$C**H**$_2$), 2.15 (1 H, m, CH$_2$C**H**$_2$), 2.47 (1 H, m, CH$_2$C**H**$_2$), 3.51 (3 H, s, OC**H**$_3$), 3.78 (3 H, s, OC**H**$_3$), 3.83 (3 H, s, OC**H**$_3$), 4.59 (1 H, m, CH$_2$C**H**-NH), 6.77 (1 H, s, Ar-H), 7.24 (1 H, d, *J*8, Ar-H), 7.37 (1 H, dd, *J*8, 2, Ar-H), 7.57 (1H, d, *J*2, Ar-H), 8.45 (1 H, d, *J*8.5, NH).

Example 2

Allocolchicine to ZD6126 Phenol

To a stirred solution of methyllithium (4 mole equivalents of a 3 M solution) in diethoxymethane and THF (3 Rel. Vols), at < -5°C, was added a slurry of allocolchicine in THF (3-7 Rel. Vols), over 1 hour. After a further 1 hour (or when no allocolchicine remained by HPLC) the mixture was treated, first with aqueous THF (3 mole equiv. water made-up to 1 Rel Vol with THF), then with water (4 Rel. Vols). Toluene (15 Rel. Vols) was then added and the aqueous layer was removed. The mixture was washed further with water (3 x 2 Rel. Vols).

mixture and was then distilled under reduced pressure to a volume of 5 Rel. Vols. A further charge of toluene (20 Rel. Vols) was then added to the mixture and it was further distilled under reduced pressure to a volume of approximately 18 Rel. Vols.

To the mixture from above, at 50°C, with stirring was added simultaneously, methane sulfonic acid (1 mol. eq.) and hydrogen peroxide (3 mol. eq.) over 1 hour. Following a further 1 hour, the mixture was quenched by the addition of sodium thiosulfate soln (1 M, 3 mol. eq.) and cooled to 20°C. Potassium hydroxide (49%, 7 mol eq.) was added and the layers were separated, retaining the lower aqueous layer. To this solution was added water (1.7 vols) and BuOAc (17 vols) and the pH was adjusted to 7 by the addition of hydrochloric acid (2.5 M). The layers were again separated, this time retaining the upper organic layer, which was washed with water wash (4.25 vols). The volume of the BuOAc solution was then reduced to approximately 8.5 Rel. Vols. by distillation under reduced pressure. Heptane (8.5 Rel. vols) was added at approximately 80°C and the mixture was cooled to 0°C over 4 hrs. The solid was filtered off, washed with a mixture of heptane and BuOAc (1.7 Rel. vols of each) then with heptane (3.4 vols) and finally dried in vacuum oven at 50 °C. Overall isolated yield of ZD6126 Phenol, form allocolchicine was approximately 75%. Data for ZD6126 Phenol: MS 358 $[M + H]^+$ (75%), 299 [M - NHCOMe] (100%); δ^H ppm (500 MHz, DMSO-D_6) 1.82-1.90 (1 H, m, CH_2**CH_2**), 1.88 (3 H, s, CO**CH_3**), 2.04-2.17 (2 H, m, **CH_2**CH_2), 2.47 (1 H, dd, *J*11.5, 5, CH_2**CH_2**), 3.46 (3 H, s, O**CH_3**), 3.77 (3 H, s, O**CH_3**), 3.82 (3 H, s, O**CH_3**), 4.44-4.50 (1 H, m, CH_2**CH**-NH), 6.69 (1 H, dd, *J*8.5, 2, Ar-H), 6.74 (1 H, s, Ar-H), 6.77 (1 H, d, *J*2.5), 7.12 (1 H, d, *J*8.5), 9.40 (1 H, s, OH).

Example 3

ZD6126 Alcohol (wherein R^2 are both methyl) to ZD6126 Phenol

To a stirred mixture of ZD6126 Alcohol in toluene (20 Rel. Vols), at 50°C, was added simultaneously, methanesulfonic acid (1 mol. eq.) and hydrogen peroxide (3 mol. eq.) over 1 hour. Following a further 1 hour, the mixture was quenched by the addition of sodium thiosulfate solution (1 M, 3 mol. eq.) and cooled to 20°C. Potassium hydroxide (49%, 7 mol eq.) was added and the layers were separated, retaining the lower aqueous layer. To this solution was added water (1.7 vols) and BuOAc (17 vols) and the pH was adjusted to 7 by the addition of hydrochloric acid (2.5 M). The layers were again separated, this time retaining the upper organic layer, which was washed with water (4.25 vols). The volume of the BuOAc solution was then reduced to approximately 8.5 Rel. Vols. by distillation under reduced

pressure. Heptane (8.5 Rel. vols) was then added at approximately 80°C and the mixture was cooled to 0°C over 4 hours. The solid was filtered off, washed with a mixture of heptane and BuOAc (1.7 Rel. vols of each) then with heptane (3.4 vols) and then dried in vacuum oven at 50°C. Isolated yield of ZD6126 Phenol, from ZD6126 Alcohol was 85.1%. Characterisation as above.

Example 4

ZD6126 Alcohol (wherein R^2 are both methyl) to ZD6126 Alkene

To a stirred mixture of ZD6126 Alcohol in THF (20 Rel. Vols), at 60°C, was added methanesulfonic acid (0.3 mol. eq.). The mixture was stirred for 9 hours, then quenched by the addition of sodium bicarbonate (0.35 mol. eq.). Water (6 vols) was added, followed by sodium chloride (solid) to cause phase separation. The upper organic layer was separated and washed with saturated brine, and the solvent was removed under reduced pressure, to provide ZD6126 Alkene as a solid. Isolated yield of ZD6126 Alkene, from ZD6126 Alcohol was approximately 84%: MS 382 $[M + H]^+$ (75%), 323 $[M - NHCOMe]^+$ (100%); δ^H ppm (500 MHz, DMSO-D_6) 1.91 (3 H, s, CCH_3), 2.05 (2 H, m, 2 x CH_2CH_2), 2.16 (3 H, s, COH_3), 2.18 (2 H, m, 2 x CH_2CH_2), 3.51 (3 H, s, OCH_3), 3.79 (3 H, s, OCH_3), 3.84 (3 H, s, OCH_3), 4.60 (1 H, ddd, *J*12.5, 3.5, 3.5, CH_2CH-NH), 5.14 (1 H, d, *J*1.5, $=CH_2$), 5.48 (1 H, d, *J*1.5, $=CH_2$), 6.79 (1 H, s, Ar-H), 7.31 (1H, d, *J*8, Ar-H), 7.43 (1H, dd, *J*8, 2, Ar-H), 7.52 (1H, d, *J*2, Ar-H), 8.45 (1H, d, *J*8.5, NH).

Example 5

ZD6126 Alcohol (wherein R^2 are both methyl) to ZD6126 Hydroperoxide

To a slurry of ZD6126 Alcohol in BuOAc (20 Rel. Vols), at 30°C, under nitrogen, was added methanesulfonic acid in water (70% w/v, 1 mole equivalent) and 30% w/v hydrogen peroxide (4 mole equivalents) was added over 1 hour. After 2 hours, the mixture was cooled to 20°C and the white solid filtered off. The solid was dissolved in a mixture of dichloromethane, methanol and hot ethyl acetate, then washed with saturated aqueous sodium bicarbonate solution, water and then saturated brine solution. The organic solution was evaporated to give ZD6126 Hydroperoxide as a white crystalline solid, in about 72% yield. $[M + H]^+$: Found 416.2103 calc for $C_{23}H_{29}NO_6$ 416.2073; δ^H ppm (500 MHz, DMSO-D_6) 1.5 (3 H, s, $CHCH_3$) 1.5 (s, 3 H, $CHCH_3$) 1.8 (1H, m) 1.9 (3 H, s, $COCH_3$) 2.0 (1 H, m) 2.1 (1 H, m) 2.5 (1 H, m) 3.5 (3 H, s, O CH_3) 3.8 (3 H, s, O CH_3 3.8 (3 H, s, O CH_3) 4.6 (1 H, ddd,

*J*11.5, 8, 8, CHN) 6.8 (1 H, s, Ar-H) 7.3 (1 H, d, *J*8, Ar-H) 7.3 (1 H, dd, *J*8, 2, Ar-H) 7.4 (1 Hd, *J*2, Ar-H) 8.4 (1 H, d, *J*8.5, Ar-H) 11.0 (1 H, s, OH); δ^C ppm (126 MHz, DMSO-D6 22.7, 26.4, 26.5, 30.2, 38.9, 48.2, 55.9, 60.6, 60.8, 82.2, 108.1, 120.1, 123.3, 124.3, 129.0, 132.5, 135.0, 139.6, 140.6, 144.3, 150.4, 152.5, 168.6.

Example 6

ZD6126 Alkene (wherein R^2 is methyl and R^1 is hydrogen) to ZD6126 Phenol

To a rapidly stirred solution of ZD6126 Alkene, in toluene (20 Rel. Vol.), at 50°C, was added simultaneously, methanesulfonic acid (1 mol. eq.) and hydrogen peroxide (3 mol. eq.) over 1 hour. Following a further 1 hour, the mixture was quenched by the addition of sodium thiosulfate solution (1 M, 3 mol. eq.) and cooled to 20°C. Potassium hydroxide (49%, 7 mol eq.) was added and the layers were separated, retaining the lower aqueous layer. To this solution was added water (1.7 vols) and BuOAc (17 vols) and the pH was adjusted to 7 by the addition of hydrochloric acid (2.5 M). The layers were again separated, this time retaining the upper organic layer, which was washed with water (4.25 vols). The volume of the BuOAc solution was then reduced to approximately 8.5 Rel. Vols. by distillation under reduced pressure. Heptane (8.5 Rel. vols) was then added at approximately 80°C and the mixture was cooled to 0°C over 4 hours. The solid was filtered off, washed with a mixture of heptane and BuOAc (1.7 Rel. vols of each) then with heptane (3.4 vols) and then dried in vacuum oven at 50°C. Yield of ZD6126 Phenol was 84%. Characterisation as above.

Example 7

ZD6126 Alcohol (wherein R^2 are both methyl) to ZD6126 Reactive Dimer (wherein R^2 are both methyl)

To a stirred solution of ZD6126 Alcohol in chlorobenzene (10 Rel. Vols), at 40°C, *para*-toluenesulfonic acid (0.40 equiv. of a 70% aq. Solution) and 50% hydrogen peroxide (1.6 eqiv.), were added over 30 minutes. The mixture was then quenched immediately by the addition of sodium thiosulfate solution (1 M, 3 mol. eq.). The organic solution contained Reactive Dimer in approximately 24% yield, as measured by HPLC. General method of isolation: The mixture is washed with potassium hydroxide (49%, 7 mol eq.), then water (1.7 vols). The remaining organic solution was then evaporated and ZD6126 Reactive Dimer is isolated from the residue by preparative HPLC. MS 797 [M + H]+ (100%), 382 (10%); δ^C ppm (126 MHz, DMSO-D6) 22.6, 26.2, 27.2, 30.1, 38.7, 48.1, 55.8, 60.4, 60.6, 81.6, 108.0,

120.2, 123.2, 124.2, 128.9, 132.6, 134.8, 139.5, 140.5, 143.9, 150.3, 152.4, 168.2; δ^H ppm (500 MHz, DMSO-D6) 1.5 (6 H, s, $CHCH_3$), 1.6 (6 H, s, $CHCH_3$), 1.80 (m, 2 H), 1.90 (6 H, s, $COCH_3$), 2.0 (2 H, m, CH_2CH_2), 2.2 (2 H, m, CH_2CH_2), 2.5 (2 H, m, CH_2CH_2), 3.5 (6 H, s, OCH_3), 3.8 (6 H, s, OCH_3), 3.8 (6 H, s, OCH_3), 4.6 (2 H, ddd, *J*12, 8.5, 7.5, CH_2CH-NH) 6.8 (2 H, s, Ar-H), 7.3 (2 H, d, *J*8, Ar-H), 7.3 (2 H, dd, *J*8, 2, Ar-H), 7.5 (2H, d, *J*2, Ar-H), 8.4 (2 H, d, *J*8.5, NH).

Example 8

ZD6126 Hydroperoxide (wherein R^2 are both methyl) to ZD6126 Phenol

To a rapidly stirred solution of ZD6126 Hydroperoxide, in toluene (20 Rel. Vol.), at 50°C, was added methanesulfonic acid (2 mol. eq.) over 5 min. Following a further 1 hour, the mixture was quenched by the addition of sodium thiosulfate solution (2 M, 3 mol. eq.) and saturated sodium bicarbonate solution (2Rel Vols.) and left to stir at ambient overnight. The solid was then filtered-off, washed with water (10 Rel Vols.) and toluene (10 Rel Vols.), then dried to give ZD6126 Phenol in 90% yield. Characterisation as above.

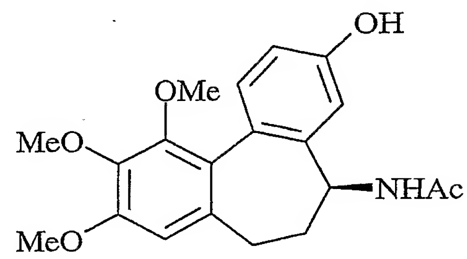
Example 9

ZD6126 Reactive Dimer (wherein R^2 are both methyl) to ZD6126 Phenol

To a rapidly stirred solution of ZD6126 Reactive Dimer, in toluene (25 Rel. Vol.), at 50°C, was added simultaneously, methanesulfonic acid (2 mol. eq.) and hydrogen peroxide (6 mol. eq.) over 3 min. Following a further 2 hours, the mixture was neutralised by the addition of triethylamine, then diluted with ethanol (30 Vols). Conversion to ZD6126 Phenol was 82%, as measured by HPLC analysis. Characterisation as above.

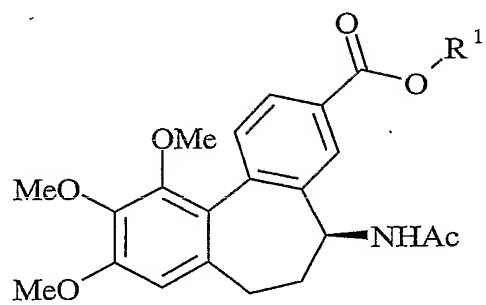
Claim

1. A process for the preparation of ZD6126 Phenol:



ZD6126 Phenol

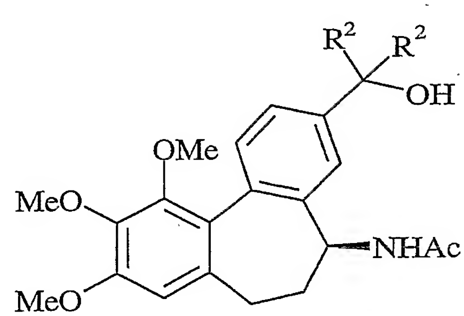
from allocolchicine or an ester derivative thereof of formula **(I)**:



(I)

wherein R^1 is C_{1-6}alkyl or aryl; which comprises:

a) reacting said allocolchicine or an ester derivative thereof of formula **(I)** with a suitable organometallic reagent and / or a suitable reducing agent; in one or more ethereal solvents to form ZD6126 Alcohol of formula **(II)**:



(II)

wherein R^2 is hydrogen, C_{1-4}alkyl or aryl; and

b) reacting ZD6126 Alcohol of formula **(II)** with an acid catalyst and an oxidising agent.